PA. _.NT COOPERATION TREAT\

	From the INTERNATIONAL BUREAU
PCT	То:
NOTIFICATION OF ELECTION (PCT Rule 61.2)	United States Patent and Trademark Office (Box PCT) Crystal Plaza 2 Washington, DC 20231 ÉTATS-UNIS D'AMÉRIQUE
Date of mailing (day/month/year)	in its capacity as elected Office
21 January 1999 (21.01.99)	
International application No. PCT/GB98/01683	Applicant's or agent's file reference N68867B GCW
International filing date (day/month/year)	Priority date (day/month/year)
09 June 1998 (09.06.98)	09 June 1997 (09.06.97)
Applicant	
BALDWIN, Thomas, John et al	
1. The designated Office is hereby notified of its election made. X in the demand filed with the International Preliminary 04 January 19: in a notice effecting later election filed with the International Preliminary 04 January 19:	y Examining Authority on: 99 (04.01.99) national Bureau on:
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Lazar Joseph Panakal

Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

Facsimile No.: (41-22) 740.14.35

From the

INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

WOODS, Geoffrey Corlett J.A. KEMP & CO. 14 South Square Gray's Inn London WC1R 5LX GRANDE BRETAGNE



NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year)

0 3. 09. 99

Applicant's or agent's file reference N.68867B GCW

International application No.

PCT/GB98/01683

International filing dato (day/month/year) 09/06/1998

Priority date (day/month/year) 09/06/1997

IMPORTANT NOTIFICATION

Applicant

MEDICAL RESEARCH COUNCIL et al.

- 1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
- 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office D-80298 Munich

Tel. +49 89 2399 - 0 Tx; 523656 epmu d

Fax: +49 89 2399 - 4465

Authorized officer

Peralt Lappas, R

Tel.+49 89 2399-8052



EL307981385US

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicants or agent's file reference N.68867B GCW	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB98/01683	International filing date (day/mole 09/06/1998	nth/year) Priority date (day/month/year) 09/06/1997
International Patent Classification (IPC) or C12N15/00	national classification and IPC	
Applicant MEDICAL RESEARCH COUNCIL	et al.	
This international preliminary exa- and is transmitted to the applicant	ทInation report has been prepar according to Article 36.	ed by this International Preliminary Examining Authority
2. This REPORT consists of a total of	of 6 sheets, including this cover	sheet.
been amended and are the bi		the description, claims and/or drawings which have containing rectifications made before this Authority tions under the PCT).
These annexes consist of a total o	f 3 sheets.	
3. This report contains indications rel	ating to the following items:	
I ⊠ Basis of the report		
II 🗆 Priority		
III D Non-establishment of	opinion with regard to novelty, in	ventive step and industrial applicability
IV Lack of unity of invention	on	
citations and explanati	ons suporting such statement	novelty, inventive step or industrial applicability;
VI		
_	nternational application	•
VIII Certain observations o	n the international application	
Date of submission of the demand	Date of	completion of this report 0 3. 09. 99
04/01/1999	1	}
Name and mailing address of the International preliminary examining authority:	d Authoriz	red officer
European Patent Office D-80299 Munich Tel. +49 89 2399 - 0 Tx: 523656	S eprnu d	AO DE MELO, T
Fax: +49 89 2399 - 4465		ne No. +49 89 2399 8972

P. 4/11 EL307981385US

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB98/01683

ı.	В	asis of the report				
1	re:	sponse to an invitati	drawn on the basis of (substitute ion under Article 14 are referred do not contain amendments.):	sheets which to in this repo	n have been furnished ort as *originally filed* a	to the receiving Office in and are not annexed to
	De	escription, pages:				·
	1-3	3,5-33	as originally filed			
	4		as received on	11/08/1999	with letter of	11/08/1999
	Cla	aims, No.:				
	2-6	5,8-22,24	as originally filed			
	1,7	,23	as received on	11/08/1999	with letter of	11/08/1999
	Dra	awings, sheets:				
	1/1	1-11/11	as originally filed			
2,	The	amendments have	resulted in the cancellation of:			
		the description,	pages:			
		the claims,	Nos.:			
		the drawings,	sheets:			
3.			en established as if (some of) the eyond the disclosure as filed (Ru		s had not been made,	since they have been

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY **EXAMINATION REPORT**

International application No. PCT/GB98/01683

V. R asoned statement under Article 35(2) with regard to novelty, inventive step or Industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes:

Claims 1-24

No:

Claims

Inventive step (IS)

Yes:

Claims 1-24

No:

Claims

Industrial applicability (IA)

Yes:

Claims 1-20 and 22-24

No:

Claims 21 (No Assessment, see section V, item 5)

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted: see separate sheet

INTERNATIONAL PRELIMINARY

International application No. PCT/GB98/01683

EXAMINATION REPORT - SEPARATE SHEET

SECTION I

1. The amended claims 1, 7 and 23 filed with your letter of 11.08.99 are considered to be allowable under Article 34 (2) (b) PCT.

SECTION V

2. Reference is made to the following documents:

D1: WO-A-94 05326

3. Novelty (Article 33(2) PCT)

> The subject-matter of the present application does not appear to be disclosed in the prior art as defined in the regulations (Rule 64 (1)-(3) PCT).

> Therefore, in view of such prior art the subject-matter of the present application (claims 1-24) has to be regarded as being new (Article 33 (2) PCT).

Inventive Step (Article 33 (3) PCT)

The closest prior art to evaluate the inventiveness of the present application (claims 1-24) is document D1.

Document D1 discloses a live vaccine strain of pathogenic bacteria, such as E. coli, comprising at least one mutation selected from a pyrimidine pathway mutation, such as in the pyrB gene, and an iron metabolism mutation, such as in the fur gene, said mutation providing attenuation of the virulence of said bacteria.

(See Abstract, page 7, line 15-page 16, line 3 and claims).

It is known in the prior art that one difficulty with the production of live attenuated vaccines is that during bulk culture the organism does not always express some proteins which are important for host protection. In addition, once such vaccines have been administered to the host, the vaccine strain does not have the optimum time or metabolic resources during its limited colonisation to express these proteins in vivo to a sufficient level to confer protection.

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INTERNATIONAL PRELIMINARY International application No. PCT/GB98/01683 EXAMINATION REPORT - SEPARATE SHEET

The <u>claimed attenuated bacteria strain differs from the one of D1</u> in that the native fur gene is modified such that its expression is regulated independently of the iron concentration in the environment of the bacteria.

Starting from D1, the underlying technical problem to be solved by the present application (claims 1-24) can be considered to lie in the provision of an alternative attenuated bacteria which produces said proteins which are important for host protection and are normally not produced in attenuated strains.

The **solution** provided by the Applicant to solve the above problem is an attenuated bacteria in which the native *fur* gene is modified such that the expression of the *fur* gene product is regulated independently of the iron concentration in the environment of the bacteria.

Neither D1 nor any of the cited prior art documents discloses nor suggests that altering the regulation of the ferric uptake regulation (*fur*) gene, such that its expression is independent of the iron concentration in the environment of the bacteria, enhances the expression of important protective antigens when the bacteria is grown in culture.

Therefore, there is no indication in the prior art that would teach the person skilled in the art to modify the native *fur* gene of attenuated bacteria, such that its expression is regulated independently of the iron concentration in the environment of the bacteria.

The attenuated bacteria of the present invention, which is the solution provided by the Applicant to solve the above problem, has thus the advantage of having increased expression of said protective antigens. Consequently live vaccines comprising said attenuated bacteria have increased efficacy when administered.

Thus, in view of the above, an inventive step can be acknowledged for the subject-matter of the present application (claims 1-24).

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INTERNATIONAL PRELIMINARY International application No. PCT/GB98/01683 EXAMINATION REPORT - SEPARATE SHEET

- 5. Industrial Applicability (Article 33(4) PCT)
- 5.1. The subject-matter of present claims 1-20 and 22-24 is susceptible of industrial applicability as defined in Article 33(4) PCT.
- 5.2. For the assessment of the present claim 21 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VII

6. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in document D1 is not mentioned in the description, nor is this document identified therein.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6:
C12N 15/00, A61K 39/095, C12R 1/36
A3
(43) International Publication Number: WO 98/56901
(43) International Publication Date: 17 December 1998 (17.12.98)

(21) International Application Number:

PCT/GB98/01683

(22) International Filing Date:

9 June 1998 (09.06.98)

(30) Priority Data:

9711964.8

9 June 1997 (09.06.97)

GB

(71) Applicant (for all designated States except US): MEDICAL RESEARCH COUNCIL [GB/GB]; 20 Park Crescent, London W1N 4AL (GB).

(72) Inventors; and

- (75) Inventors/Applicants (for US only): BALDWIN, Thomas, John [GB/GB]; Institute of Infections & Immunity, University Hospital, Nottingham NG7 2UH (GB). BORRIELLO, Saverio, Peter [GB/GB]; Public Health Laboratory Service, Central Public Health Laboratory, 61 Colindale Avenue, London NW9 5HT (GB). PALMER, Helen, Mary [GB/GB]; Public Health Laboratory Service, Bristol Royal Infirmary, Mariborough Street, Bristol BS2 8HW (GB).
- (74) Agent: WOODS, Geoffrey, Corlett; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(88) Date of publication of the international search report: 18 March 1999 (18.03.99)

(54) Title: LIVE ATTENUATED VACCINES

(57) Abstract

An attenuated bacterium in which the native *fur* gene, or homologue thereof, is modified such that the expression of the *fur* gene product, or homologue thereof, is regulated independently of the iron concentration in the environment of the bacterium, is suitable for use as a live vaccine. The bacterium may be, in particular, *Neisseria meningitidis*.

FOR THE PURPOSES OF INFORMATION ONLY

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l							
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DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

ational Application No PCT/GB 98/01683

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C12N15/00 A61K39/095 C12R1/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 6 C12N A61K C12R

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT					
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to daim No.			
X	WO 94 05326 A (UNIV SASKATCHEWAN) 17 March 1994 see abstract	1-3,5-7, 19-24			
	see page 7, line 15 - page 8, line 18 see page 11, line 4 - line 8				
	see page 12, line 6 - line 13	·			
	see page 12, line 20 - line 22 see claims	;			
A	WO 87 02678 A (OREGON STATE) 7 May 1987 see abstract see page 1, line 1 - page 2, line 17 see page 3, line 6 - line 27	1-5,19			
Α	EP 0 322 237 A (WELLCOME FOUND) 28 June 1989 see abstract	3,5,6, 15.16			
	-/				

X Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filling date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filling date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
Date of the actual completion of the international search	Date of mailing of the international search report
18 December 1998	12/01/1999
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk	Authorized officer
Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Fax: (+31-70) 340-3016	Panzica, G

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tr. ational Application No PCT/GB 98/01683

:.(Continue	ation) DOCUMENTS CONSIDERED TO BE RELEVANT		
ategory °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	
	PINTOR M. ET AL.: "Blocking of iron uptake from transferrin by antibodies against the transferrin binding proteins in Neisseria meningitidis" MICROBIAL PATHOGENESIS, vol. 20, no. 3, 1996, pages 127-139, XP002085216 see abstract	1-5,15, 16,19-21	
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...ternational application No.

PCT/GB 98/01683

Box I Observation where certain claims were found unsearchable (Continuation of item 1 f first she t)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: 20, 21 because they relate to subject matter not required to be searched by this Authority, namely: Remark: Although claim(s) 20 and 21 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking(Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

Information on patent family members

In .tional Application No PCT/GB 98/01683

	tent document I in search repor	t	Publication date		Patent family member(s)	Publication date
WO	9405326	A	17-03-1994	AT	173166 T	15-11-1998
				AU	683221 B	06-11-1997
				AU	4939193 A	29-03-1994
				DE	69322092 D	17-12-1998
			,	EP	0659086 A	28-06-1995
	÷			IL	106903 A	10-01-1997
			·	US	5747309 A	05-05-1998
WO	8702678	Α	07-05-1987	US	4681761 A	21-07-1987
				AU	594400 B	08-03-1990
				AU	6623286 A	19-05-1987
				EP	0245433 A	19-11-1987
				JP	63502427 T	14-09-1988
EP	0322237	Α	28-06-1989	AU	2919389 A	19-07-1989
				CA	1327331 A	01-03-1994
				DE	3888652 D	28-04-1994
			• .	DE	3888652 T	07-07-1994
			·	DK	412689 A	22-08-1989
		•		ES	2061700 T	16-12-1994
				WO	8905856 A	29-06-1989
			,	ΙE	65176 B	04-10-1995
				IL	88766 A	31-07-1995
	•			JP	2602970 B	23-04-1997
				JP	2502785 T	06-09-1990
				KR	9710759 B	30-06-1997
				US	5811105 A	22-09-1998
				US	5770214 A	23-06-1998

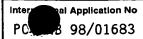


(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference		ation of Transmittal of International Search Report [/ISA/220) as well as, where applicable, item 5 below.
N68867B GCW International application No.	International filing date (day/month/ye	ar) (Earliest) Priority Date (day/month/year)
PCT/GB 98/01683	09/06/1998	09/06/1997
Applicant		
MEDICAL RESEARCH COUNCIL	et al.	
This International Search Report has been according to Article 18. A copy is being tra		ng Authority and is transmitted to the applicant
This International Search Report consists X It is also accompanied by a copy	of a total of sheets y of each prior art document cited in this	
1. 【X】 Certain claims were found un	searchable(see Box I).	
2. Unity of Invention is lacking(s	ee Box II).	
	ntains disclosure of a nucleotide and/o out on the basis of the sequence listing	r amino acid sequence listing and the
	I with the international application.	
X furn	ished by the applicant separately from	he international application,
[nt to the effect that it did not include e in the international application as filed.
Trai	nscribed by this Authority	
4. With regard to the title, X the	text is approved as submitted by the ap	plicant
the	text has been established by this Autho	rity to read as follows:
1		
5. With regard to the abstract,		
	text is approved as submitted by the ap	Pule 38.2(b), by this Authority as it appears in
Box		h from the date of mailing of this International
6. The figure of the drawings to be publ	ished with the abstract is:	
	suggested by the applicant.	X None of the figures.
I	ause the applicant failed to suggest a fi	
bec	ause this figure better characterizes the	invention.



Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely: Remark: Although claim(s) 20 and 21 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. 2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.



A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/00 A61K39/095 C12R1/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 $\begin{array}{ll} \mbox{Minimum documentation searched (classification system followed by classification symbols)} \\ \mbox{IPC 6} & \mbox{C12N} & \mbox{A61K} & \mbox{C12R} \\ \end{array}$

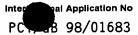
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 05326 A (UNIV SASKATCHEWAN) 17 March 1994 see abstract see page 7, line 15 - page 8, line 18 see page 11, line 4 - line 8 see page 12, line 6 - line 13 see page 12, line 20 - line 22 see claims	1-3,5-7, 19-24
Α	WO 87 02678 A (OREGON STATE) 7 May 1987 see abstract see page 1, line 1 - page 2, line 17 see page 3, line 6 - line 27	1-5,19
Α	EP 0 322 237 A (WELLCOME FOUND) 28 June 1989 see abstract/	3,5,6, 15,16

Further documents are listed in the continuation of box C.	Patent family members are listed in annex.			
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family			
Date of the actual completion of the international search 18 December 1998	Date of mailing of the international search report $12/01/1999$			
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Panzica, G			

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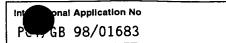


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